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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,541	ESHLEMAN ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,11-13,23,28-30,40-42 and 75-86* is/are pending in the application.

4a) Of the above claim(s) *1-5,23,28-30,40-42,75 and 76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,11-13 and 77-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6, 11-13, 23, 28-30, 40-42, and 75-86 are pending.

Claims 1-5, 23, 28-30, 40-42, 75 and 76 are withdrawn from examination as detailed in the Office Action of 12/16/2008.

Claims 6, 11-13 and 77-86 are examined on the merits.

This Office Action is in reply to Applicants' correspondence of 03/24/2010.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

Please Note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

1. It is noted that Applicants have elected for the examination of claims as they require the particular KRAS2 mutation that is G35A, where the instant claims encompass non-elected subcombinations in the recitation "at least one of a G35A, a G35T, or a G34C". No claim is indicated as allowed in this Office Action. Prior to the allowance of the application any non-elected subject matter which has not been rejoined with the elected subject matter will be required to be deleted from the claims.

Withdrawn Claim Objections

2. The objection to claim 10, as set forth on page 3 of the Office Action of 12/24/2009, is **WITHDRAWN** in light of the cancellation of claim 10.

The objection to claim 6, as set forth on page 4 of the Office Action of 12/24/2009, is **WITHDRAWN** in light of the amendments to claim 6.

Withdrawn Claim Rejections - 35 USC § 112 1st ¶ - Scope of Enablement

3. The rejection of claims under 35 U.S.C. 112, first paragraph, as set forth on pages 4-7 of the Office Action of 12/24/2009, for encompassing non-enabled scope, is **WITHDRAWN** in light of the amendments to the claims.

Withdrawn Claim Rejections - 35 USC § 103

4. The rejections of claims under 35 USC 103 as obvious in view of the prior art, as set forth on pages 8-13 of the Office Action of 12/24/2009, are **WITHDRAWN** in light of the amendments to the claims.

New Claim Rejections - 35 USC § 103
Newly applied to claims as necessitated by amendments

5. Claims 6, 11-13, 77-81and 84-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schouten et al (2002), as cited on the IDS of 08/25/2006, in view of Watanabe et al (1999).

With regard to the limitations of claim 6, Schouten et al (summarized in Fig.2 on p.4, and Fig 8 on p.11) teaches a method that comprises contacting a nucleic acid sample with a pair of oligonucleotides in which each of the oligonucleotides has a gene

specific region (termed 'hybridisation sequence' in the reference) and a primer region (termed 'PCR primer sequence Y' and 'PCR primer sequence X' in the reference). The reference indicates that mutation detection can be accomplished by using a nucleotide difference (as compared to the target nucleic acid sequence) in the gene specific region of one oligonucleotide (p.11, right col., lns.5-10). The method steps of the reference indicate that the primers of the pair are suitable for ligation to one another (p.2, right col., ln.1). Furthermore the reference teaches a ligation reaction and amplification of the formed ligation product (p.2, right col., ln.1-23). The reference teaches analyzing the reaction product (Fig 3). Schouten et al also teaches that reaction products may be quantified (e.g.: p.2 – Results).

Regarding claims 80 and 81, Schouten et al teaches that primers contain a stuffer sequence of varying length (Fig 2), where a stuffer sequence is a foreign DNA region between the gene specific sequence and the primer region (relevant to claim 80), and allows detection of the particular amplicon (e.g. Fig 8 legend) thus acting as a probe (relevant to claim 81).

Relevant to claims 84-86, the method of Schouten et al provides the same methodoligcal steps as the methods of the rejected claims, and Schouten et al teaches that the MPLA method is particularly sensitive (e.g.: p.12- left col.; p.13 - Conclusion). As such, the method of Schouten et al is a method wherein particular sequences at levels of 10%, 1%, and 0.1% or less can de detected.

Schouten et al does not specify the analysis of a G35A KRAS mutation, nor that a G35A KRAS mutation level equal to mutant/(mutant + wild-type) is indicative of a phenotype.

However, the quantitation of the G35A mutation in KRAS2 and the use of determined quantities to differentiate pancreatic cancer and chronic pancreatitis was well known in the art at the time the invention was made.

Watanabe et al teaches the analysis of mutations in differentiating between pancreatic cancer and chronic pancreatitis.

Relevant to claims 6 and 13, Watanabe et al teaches the analysis of the G35A mutations of the KRAS2 gene (e.g.: p.344 – Mutational types of KRM in PPJ by PCR-HPA; Watanabe et al references the G35A mutation as a GAT (Asp) codon in Tables 1 and 3). Relevant to the limitations of claim 6, a mutation analyzed by the methods of Watanabe et al is the same G35A mutation of the instant specification (e.g. Fig 1 of Watanabe et al references codon 12). Relevant to claim 13, the quantitative analysis of mutation content provided by Watanabe et al (e.g.: Fig 1; Table 3) is determining a KRAS mutation level and analysis of mutations in the PPJ and surgical material of a subject (e.g.: Table 3) is monitoring KRAS mutation levels (relevant to claim 13).

Relevant to the limitations of claims 11 and 12, Watanabe et al teaches that the quantitated level of KRAS2 of the KRAS2 G35A mutation is indicative of pancreatic cancer as opposed to chronic pancreatitis (p.552 – KRAS2 mutations in circulating DNA; p.551 - Abstract)., where increased levels of mutations are indicative of cancer versus decreased levels of mutations are indicative of pancreatitis (e.g.: Fig 1; p.346,

left col.). With regard to the limitations of claims 11 and 12, the teachings of Watanabe et al (specifically that increased levels of mutations are indicative of cancer, and decreased levels of mutations are indicative of pancreatitis) indicate that a mutation level of 0.0% (e.g. undetected KRAS2 mutation) is indicative of chronic pancreatitis (claim 11), and a mutation level of 100% (e.g. KRAS2 mutation detected in all samples from a subject) is indicative of pancreatic cancer (claim 12).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Schouten et al for the quantitative analysis of the G345A mutation as taught by Watanabe et al to differentiate the presence of pancreatic cancer from pancreatitis. One would have been motivated to analyze the mutation of Watanabe et al based on the assertion of Watanabe et al that such an analysis is useful as a cancer diagnostic (p.345 - Discussion). With regard to the limitation of claim 6 that a mutation level is equal to mutant/(mutant + wildtype), it is noted that Schouten et al teaches a similar calculation in detection of particular sequences (e.g.: Table 1 legend), and Watanabe et al teaches methods wherein both mutant and wildtype quantities are determined in samples (e.g.: Table 3). As such where the skilled artisan would be aware of various methods for numerically recording a level of detected mutation, given the particular teachings of the cited prior art, a method wherein the recorded level is equal to mutant/(mutant + wildtype) (i.e.: mutation level equals percentage of total) is rendered obvious by the prior art.

With regard to the limitations of claims 77-79, requiring sensitivity levels of 76%, 88%, and 94%, respectively, Watanabe et al specifically teaches that by setting different

mutation levels as thresholds and cutoffs one can achieve different levels of sensitivity and specificity (e.g.: p.343 – The levels of chemiluminescence in PPJ from patients with PCa, CP, and the control group by PCR-HPA; Fig. 1; p.346 – left col.). In the instant case, relevant to the teachings of Watanabe et al and the limitations of claims 77-79, the MPEP provides "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have set different cutoffs and thresholds, as taught by Watanabe et al, to achieve different sensitivities and specificities.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 103 as obvious in view of the prior art cited in the Office Action of 12/24/2009. It is noted that the rejections set forth in the previous Office Action have been withdrawn in light of the amendment to the claims, and new rejections citing different prior art are set forth in the instant Office Action. Applicants arguments of 03/24/2010 are addressed as they are relevant to the instantly set forth rejections.

Applicants have argued that the instantly claimed methods include the definition of 'mutation level', as imported from the specification, to require the calculation mutated/(mutated + wild type). As set forth in the rejection, determining such a level is rendered obvious by the teaching of Schouten t al in combination with the newly cited Watanabe et al, where in particular Watanabe et al teaches that a combination of both mutant and wild type KRAS is detected in pancreatic juice, where one can establish a threshold cutoff to differentiate the amount of mutant that is found in cancer versus pancreatitis. This teaching, as provided by Watanabe et al, is particularly relevant to Applicants arguments concerning the claimed methods, where the teachings of the instantly cited prior art provide for detection of a level of KRAS mutation as indicative of a particular phenotype.

New Claim Rejections - 35 USC § 103

6. Claims 82 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schouten et al (2002), as cited on the IDS of 08/25/2006, in view of Watanabe et al

(1998), as previously applied to claims 6, 11-13, 77-81, and 84-86, and further in view of Nazarenko et al (2002).

The teachings of Schouten et al in view of Watanabe et al are applied to claims 82 and 83 as they were previously applied to claims 82 and 83 as they were previously applied to claims 6, 11-13, 77-81 and 84-86.

Schouten et al in view of Watanabe et al does not specifically provide for quantitative or real time amplification (claim 82) or multiplex amplification (claim 83). However, such methods were well known in the art at the time the invention was made and are taught by Nazarenko et al.

Nazarenko et al provides methods that include quantitative real time PCR in a multiplex format.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Nazarenko et al for the detection methods as rendered obvious by Schouten et al in view of Watanabe et al. The skilled artisan would have been motivated to us the methods of Nazarenko et al based on the teaching of Nazarenko et al that such methods are efficient, reliable, and cost-effective (p.2, left col.).

Conclusion

7. No claim is allowed. No claim is free of the teachings of the prior art.

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date

of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634